

INTRALESIONAL INJECTION OF ETHANOLAMINE OLEATE WITH OR WITHOUT LOCAL ANAESTHETIC AGENT TO ASSESS POSTOPERATIVE PAIN IN ORAL VENOUS MALFORMATIONS (A RANDOMIZED CONTROLLED CLINICAL TRIAL)

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ABSTRACT

INTRODUCTION: Sclerotherapy is an established treatment modality for oral vascular anomalies. A sclerosing agent such as Ethanolamine Oleate has been widely used for oral vascular malformation, especially low-flow venous lesions, however, pain is one of the most common postoperative complications. Therefore, Ethanolamine Oleate with an anesthetic agent may help in reducing postoperative pain in cases of oral venous malformation.

AIM OF THE STUDY: To compare the effect of Ethanolamine Oleate as a sclerosing agent for oral venous malformation with and without an anesthetic agent in reducing postoperative pain and resolution of the lesion.

MATERIALS AND METHODS: 16 patients with oral venous malformation were recruited and randomly allocated into two equal groups. Sclerotherapy with Ethanolamine Oleate was performed for all patients in Group A (Control Group) eight patients were injected with Ethanolamine Oleate alone and for Group B (Study Group) eight patients were injected with Ethanolamine Oleate mixed with Lidocaine.

RESULTS: There was a statistically significant decrease between the two studied groups. Using the VAS scale, showed a significant decrease in post-operative pain reaching an (87.5%) success rate in Group B, especially two days postoperatively.

CONCLUSION: This study confirmed the positive effect of intralesional injection of EO and Lidocaine in OVMs regarding postoperative pain and resolution of the lesion.

KEYWORDS: Ethanolamine Oleate, Anesthesia, Oral Venous Malformation, Sclerotherapy, pain.

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INTRODUCTION

Vascular anomalies (VAs) are classified according to the Mulliken and Glowacki classification (1982) and are caused by blood vessel abnormalities or endothelial proliferation (1). Oral Venous Malformations (OVMs) can be categorized into high-flow (arterial or arteriovenous component) and low-flow (venous, capillary, or lymphatic component) (2).

Most of OVMs in the oral cavity are venous and low flow in nature, expanding into single or multiple. The lips, tongue, buccal mucosa, and palate are the main affected areas. Signs and symptoms of OVMs include pain, ulcerations, bleeding, discomfort, and cosmetic disturbance (3). OVMs are usually present from birth and are

triggered by trauma, pregnancy, or hormonal factors (4).

Treatment is essential when personal discomfort, clinical symptoms, or cosmetic disturbance arise, therefore different treatment options were introduced, which include the traditional approach such as surgery, to newer approaches such as sclerotherapy, corticosteroids, laser, and cryotherapy (5).

Sclerotherapy is an effective and conventional procedure for curing OVMs. It is a straightforward method that involves an intralesional injection, allowing good esthetic results, a low recurrence rate, and adequate morbidity (6).

Ethanolamine Oleate (EO) is a sclerosing agent characterized by low toxic effects and high efficacy. Therefore it is a safe and efficient

sclerosing agent that can be used in the treatment of VAs in various regions inside and outside the oral cavity (7).

EO is composed of a synthetic mixture of Oleic Acid and Ethanolamine. EO causes an acute inflammatory reaction of the intimal endothelium of the vein which leads to scarring at the inner wall of the veins and possible closure of the veins (8).

Adverse reactions related to EO include pain, inflammation, redness, tissue necrosis, and even allergic reaction have been reported (9).

To provide an efficacious, secure, and timeless treatment of OVMs, it is essential to establish the optimal concentration of EO and prevent or reduce side effects such as rash, edema, pain, bleeding, ulceration, or necrosis (10)

Lidocaine is one of the very well-known safe and potent anesthetic agents with an analgesic characteristic (11), thus it may show effective results in post-operative pain management.

Since EO causes post-operative pain, the purpose of this study was to introduce a novel approach of intralesional injection with both EO with Lidocaine to reduce post-operative pain and compare both clinically and by Ultrasound Doppler imaging, the effect on OVMs.

MATERIALS AND METHODS

Study sample and setting

This was a randomized controlled parallel-group clinical trial set up and reported according to the CONSORT guidelines (12). After the approval of the research ethics committee, 16 patients were recruited from outpatient clinics of the maxillofacial department Faculty of Dentistry at Alexandria University.

Patients grouping

Group A (Control group) Eight patients with OVMs were injected with EO alone, while **Group B (Study group)** Eight patients with OVMs were injected with EO mixed with Lidocaine.

Eligibility criteria

The criteria for including patients were as follows, inclusion criteria included females and males of varying ages from child to an adult suffering from OVMs with a size of 2-4cm, while the exclusion criteria included patients with high-flow OVMs and patients medication-interfering with wound healing (e.g., steroids, bisphosphonates, anticoagulants) or specific states preventing the use of EO (e.g., pregnancy, lactation).

General Examination

Clinical examination was done via inspection to evaluate the size, location, and degree of swelling of OVMs, and asymmetry via palpation to assess any tenderness and the teeth' mobility. While radiological examination Doppler ultrasound (GE Voluson ultrasound, Kpi healthcare, USA) was done for each patient to validate the diagnosis and determine the flow, size, and spread of the lesion.

Materials

Ethanolamine Oleate (EGYPTIAN INT. PHARMACEUTICALS INDUSTRIES. CO (EIPICO) – EGYPT) and Lidocaine Vials (PHARCO PHARMACEUTICALS – EGYPT) were used. (Figure 1)

Sclerotherapy Method

OVMs lesions were disinfected with an anti-septic solution (Betadine) (Nile company for pharma, Chemical Ind, Egypt) before injection to avoid contamination and the spread of infection (Figure 2). A local anesthetic nerve block was given according to the lesions' locations. Using the doppler ultrasound report and a dental caliper, lesion sizes were confirmed, and accordingly, the amount of EO and Lidocaine to be mixed and injected was calculated at a 2:1 ratio following the protocol described by Johann et al. (2005) (13) and Costa et al. (2011) (14) A concentration of 5% and a volume of EO of 1 ml to every 1mm lesion size were used (Figure 3). A short insulin needle and a syringe were used for the application of EO and Lidocaine. Blood was aspirated to determine if the needle was inserted into the vascular lumen. After injection, the pressure was applied using gauze for 3 minutes to stop the reflux of EO. OVMs presented at the tongue were sutured just 1mm behind to avoid the spread of sclerosing agent to normal tissue (Figure 4). Injections were repeated biweekly till the lesion is clinically invisible and with Doppler Ultrasound confirmation of no flow inside the lesion.

Follow-up phase Clinical evaluation

Clinical Parameters

The pain intensity was evaluated after the 1st, 2nd, and 5th day after each injection postoperative using the Visual Analogue Scale (VAS). The VAS consists of a 10cm line, with two endpoints representing 0 ('no pain') and 10 ('pain as bad as it could be), the patient was asked to rate their current degree of pain by placing a mark on the line (15).

Edema was evaluated after each injection's ability to pit after the 1st, 2nd, and 5th day. The examiner's fingers pressed into a dependent lesion for 5 seconds. The finger sank into the tissues and leaves an impression when it was removed. The pitting was graded on a scale of +1 to +4. Grade +1: up to 2mm of depression, rebounding immediately. Grade +2: 3–4mm of depression, rebounding in 15 seconds or less. Grade +3: 5–6mm of depression, rebounding in 60 seconds. Grade +4: 8mm of depression, rebounding in 2–3 minutes (16).

The size was measured before and after each injection using a dental caliper and confirmed by the doppler ultrasound report. Doppler ultrasound was done after the last session of injection on each patient to confirm the resolution of the lesion and compare the size before and after treatment.

All patients were followed up for 3 months until the complete resolution of the lesions.

Statistical analysis

Data were collected and entered as numerical or categorical, to the computer using Statistical Package for Social Science (SPSS) program for statistical analysis (IBM Corp., Armonk, New York) (17). Data were described using minimum, maximum, median, 95% CI of the median, and 25th to 75th percentile (18). Comparisons were made between two independent, not-normally distributed subgroups using the Mann-Whitney U test (19). Comparisons were carried out among related samples by Friedman's test (20). Pair-wise comparison when Friedman's test was significant was carried out using the Dunn-Sidak method (21,22). During sample size calculation, beta error accepted up to 20% with a power of study of 80%. Statistical significance was tested at a p-value <.05 (23).



Figure (1): EO and Lidocaine Vials.

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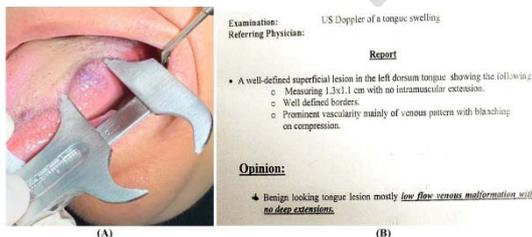


Figure (2): Diagnostic tools. (A) measuring of oral venous malformation size using a caliper, (B) Doppler Ultrasound report describing the lesion's location, size, and flow.



(A)



(B)



(C)



(D)



(E)

Figure (3): Patient from Group A showing (A) disinfection of the lesion by anti-septic solution, (B) patient with oral venous malformation at buccal mucosa in front of the lateral and canine teeth, (C) patient getting injected with Ethanolamine Oleate only, (D) patient after complete resolution of oral venous malformation.

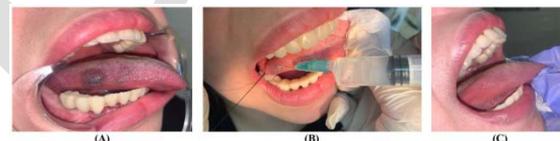


Figure (4): Patient from Group B showing (A) oral venous malformation on the right lateral surface of the tongue, a (B) patient getting injected by EO and Lidocaine, tongue sutured just 1mm behind oral venous malformation, (C) patient after complete resolution of oral venous malformation. and the whiskers represent the minimum and maximum after excluding outliers (black-filled circles).

RESULTS

This study included 16 patients with oral venous malformations, 8 patients were injected with EO alone (Group A) while the other 8 patients were injected with EO mixed with Lidocaine (Group B).

Age

The age of Group A patients ranged from 19 -70 years old with a median of 42 years, while in Group B patients it ranged from 9 - 60 years old with a median of 37 years. Thus, there was no statistically significant difference between the two studied groups.

Gender

In each group males and females were equally 4/8 (50%) represented, therefore there was no sex predilection.

Size of oral venous malformations after Intervention (mm)

In each group, repeated measures analysis showed a statistically significant change in size among the different points of measurement in Group A ($p < .001$) and Group B ($p < .001$).

Using Pairwise comparisons of groups, Group A showed a statistically significant decrease in Size on the fifth day when compared with the first day ($p = .001$) and when compared with the second day ($p < .001$). In Group B the size showed a statistically significant decrease on the fifth day when compared with the first day ($p = .031$) and when compared with the second day ($p = .001$).

Group A and B patients showed a statistically significant decrease in size on the 5th day compared with the 1st and 2nd day. Therefore, the lesion size gets bigger in the first few days due to the sclerosing agent volume, until the lesion gradually resolves.

Edema scale

In each group, repeated measures analysis showed a statistically significant change in the Edema Scale among the different points of measurement in Group A ($p < .001$) and Group B ($p < .001$).

Using Pairwise comparisons of groups, Group A showed a statistically significant decrease in Edema Scale on the fifth day when compared with the first day ($p < .001$) while there was no statistically significant decrease in Edema Scale compared with the first day ($p = .102$) and with the second day ($p = .051$). Group B, Edema Scale showed a statistically significant decrease in Edema Scale on the fifth day when compared with the first day ($p = .004$) while there was no statistically significant decrease in Edema Scale compared with the first day ($p = .190$) and with the second day ($p = .555$).

Correlating with the size of the lesion results, Groups A and B showed a statistically significant decrease in edema on the 5th day.

VAS score (Table 1, Figure 5)

First Day: The VAS in Group A ranged from 5.00-8.00 with a median [25th-75th percentile] of 7.00 [6.00-7.50], 95% Confident Interval (CI) was 7.00-8.00, while in Group B it ranged from 2.00-9.00 with a median [25th-75th percentile] of 4.00 [3.00-5.50], 95% Confident Interval was 3.00-6.00. There was a statistically significant difference between the two studied groups ($p < .001$).

Second Day: The VAS in Group A ranged from 2.00-8.00 with a median [25th-75th percentile] of 6.00 [4.50-7.00], 95% Confident Interval (CI) was 5.00-7.00, while in Group B it ranged from 1.00-6.00 with a median [25th-75th percentile] of 2.50 [2.00-3.50], 95% Confident Interval was 2.00-3.00. There was a statistically significant difference between the two studied groups ($p < .001$).

Fifth Day: The VAS in Group A ranged from 0.00-7.00 with a median [25th-75th percentile] of 2.00 [1.00-3.00], 95% Confident Interval (CI) was 2.00-3.00, while in Group B it ranged from 0.00-5.00 with a median [25th-75th percentile] of 2.00 [1.00-2.50], 95% Confident Interval was 2.00-3.00. There was no statistically significant difference between the two studied groups ($p = .245$).

In each group, repeated measures analysis showed a statistically significant change in VAS among the different points of measurement in the EO patient group ($p < .001$) and EO + lidocaine patient group ($p < .001$).

Using Pairwise comparisons of groups, Group A showed a statistically significant decrease in VAS on the fifth day when compared with the first day ($p < .001$) and with the second day ($p = .003$). Group B showed a statistically significant decrease in VAS on the fifth day when compared with the first day ($p < .001$) while there was a statistically significant decrease in VAS on the second day compared with the first day ($p = .008$).

There was a statistically significant decrease in VAS in Group B compared to Group A patients, especially on the fifth day when compared with the first and second days.

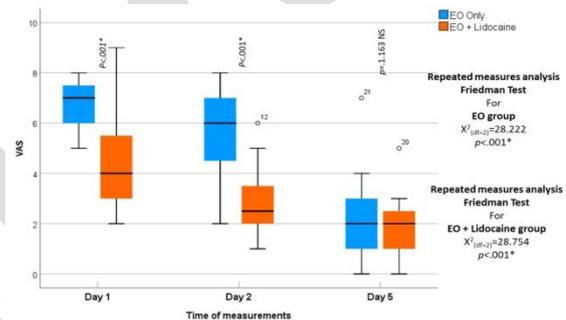


Figure (5): Box and whisker graph of VAS in the studied groups, the thick line in the middle of the box represents the median, the box represents the interquartile range (from 25th to 75th percentiles),

Table (1): Showing VAS results on 1st, 2nd and 5th days in both groups

Vas	Group		Test of significance p value
	EO only (n=16)	EO + Lidocaine (n=16)	
First Day Min. – Max. Median 95% CI of the median 25 th Percentile –75 th Percentile	5.00-8.00 8.00 7.00 7.00-8.00 8.00 6.00-7.50	2.00-9.00 4.00 3.00-6.00 3.00-5.50	$\chi^2_{(MW)} = 3.63$ 9 $p < .001^*$
Second Day Min. – Max. Median 95% CI of the median 25 th Percentile	2.00-8.00 8.00 6.00 5.00-7.00	1.00-6.00 2.50 2.00-3.00 2.00-3.50	$\chi^2_{(MW)} = 3.78$ 5 $p < .001^*$

-75 th Percentile	4.50-7.00		
Fifth Day Min. – Max. Median 95% CI of the median 25 th Percentile –75 th Percentile	0.00-7.00 2.00 2.00-3.00 1.00-3.00	0.00-5.00 2.00 1.00-2.50	$\chi^2_{(MW)}=1.16$ 3 $p=.245$ NS
Friedman Test of significance p value	$\chi^2_{(df=2)} = 28.222$ $p < .001^*$	$\chi^2_{(df=2)} = 28.754$ $P < .001^*$	
Percentage change (1 st day vs 2 nd day) Min. – Max. Median 95% CI of the median 25 th Percentile –75 th Percentile	-60.00 - 16.67 -14.29 -16.67 - 0.00 -28.57 - -12.50	-66.67 - 0.00 -33.33 -33.33 - 25.00 -50.00 - 25.00	$\chi^2_{(MW)}=2.84$ 8 $p=.004^*$
Percentage change (2 nd day vs 5 th day) Min. – Max. Median 95% CI of the median 25 th Percentile –75 th Percentile	-100.00 - -12.50 -58.57 - -75.00 -50.00 - -75.00 -50.00	-100.00 - 50.00 -36.67 - -50.00 -50.00 - -50.00 20.83	$\chi^2_{(MW)}=2.16$ 4 $p=.030^*$

n: number of patients
 Min-Max: Minimum to Maximum
 CI: Confidence interval
 MW = Mann-Whitney U
 p: Probability of error (chance)
 *: Statistically significant ($p < .05$)
 NS: Statistically not significant ($p \geq .05$)

DISCUSSION

This study intended to evaluate clinically and by Doppler Ultrasound, the treatment of OVMs, and the effect of EO injection alone versus EO injection with Lidocaine on postoperative pain reduction.

There was no statistically significant difference in age, although the lesion may be found at birth or develop in childhood or adolescence with a prevalence in the second decade (24). A reduced inflammatory response was observed in the elderly due to the physiological aging process (25).

There was also no statistically significant difference in sex among the patients, even though OVMs are more frequent in females. Jackson et al. (1993) observed a female: male ratio of 4:1 in patients (26), while Barrett et al. (2000) observed that OVMs affect equally females and males, as in our study (27).

EO showed positive results in decreasing the lesion size. It was observed that a complete resolution requires more than one session since the complete fibrotic reaction process takes time, especially larger lesions that may need more sessions and higher volume. This was confirmed when 1 out of 8 patients in Group B (12.5%), had the biggest lesion size and therefore had to undergo more than two injection sessions, surgical

debulking, and even fractional laser to minimize the size and pigmentation. Although EO causes swelling of the lesions, which may persist for a few days, it starts resolving at the 5th-day mark.

Most patients in Group B compared to Group A, using the VAS scale, showed a significant decrease in post-operative pain reaching an (87.5%) success rate. The addition of lidocaine with EO injection has shown positive results in decreasing pain, especially two days post-operatively unlike if it was injected alone, it took up to at least 5 days postoperatively for the pain to completely vanish.

Ideal EO concentration and dosing for treatment are still debatable. Manzano et al. (2019) reported that concentrations of 1.5% and 2.5% are effective (28). EO 5% concentration with Lidocaine at a 2:1 ratio has shown to be more effective for the complete resolution of lesions and decrease post-operative pain.

OVMs were found on the buccal mucosa, lips, and palate but mostly on the tongue (75%), whilst Couto et al. (2019) reported, the lower lip is the most common site (81%) (29). One reason may explain, why patients with lip lesions seek dermatologists or plastic surgeons' intervention rather than maxillofacial surgeons, more frequently than patients with lesions in other areas.

Most patients in Group A and Group B had an excellent response to EO, providing complete resolution of the lesion, with a success rate of (93.75%), correlating with Puche-Torres et al. (2010) reporting a success rate of 95.24% of treatment (30). Although the exception of 1 out of 8 patients in Group B (12.5%), recurrence of OVM has been described after the follow-up period from injection sessions. Although it is considered to be a rare complication, Álvarez-Camino et al. (2013) reported, that 1 out of 10 patients (10%) lesion has indeed returned (31). A different type of sclerosing may exclude possible EO resistance and allow better closure of the lesion and faster healing.

The patient's chief complaints of discomfort while eating, speaking and talking always completely vanished after lesion resolution, with function back to normal. While the color of the lesions was initially blue, when completely resolved showed a pink normal color.

In Group A, 1 out of 8 patients (12.5%), had an unexpected allergy to the sclerosing agent with abnormal swelling, correlating with the complications observed in a previous study, Ierardi et al. (2010) reported that 1 out of 15 patients (18.75%) experienced Angioedema (32). The patient was administered corticosteroids to treat the hypersensitivity, however, there were no further symptoms of discomfort or pain after complete lesion resolution.

CONCLUSIONS

Overall, this study confirmed the positive effect of intralesional injection with EO when mixed with lidocaine in lesion resolution and postoperative pain which has significantly minimized in Group B compared to Group A. Although more studies may be required, this novel approach validates a better, pain-free, and faster treatment process when treating OVMs.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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